Unique Protocol ID: 1332356
Brief Title: Assessment of Methadone and Buprenorphine in Interstitial Fluid
Official Title: Interstitial Fluid Collection Validation Study
NCT number : NCT05546229
IRB Protocol document submittal date : July 19 2023
IRB final approval date : August 3 2023

Interstitial Fluid Collection Validation Study
IRB Research Proposal
Protocol #002
July 19, 2022

BACKGROUND INFORMATION

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INTRODUCTION

A. Type of Research

Pilot Study

B. Purpose/Objective of the Study

This pilot study is an exploratory feasibility study that aims to determine if common medications for opioid use disorder (OUD; i.e., buprenorphine, methadone) and their metabolites (i.e., norbuprenorphine [a metabolite of buprenorphine], buprenorphine-3-glucuronide [B3G; a metabolite in buprenorphine], ethylidene dimethyl diphenyl pyrrolidine [EDDP; a metabolite for methadone]), can be detected in dermal interstitial fluid (ISF). Similar to our previous ISF study approved by WCG IRB and completed in 2021 (IRB Tracking ID 20214878), microliter volumes of ISF from the surface of the skin will be collected from patients with a prescription for each these medications (buprenorphine n = 10; methadone n = 10) and controls (n=2) using a microneedle patch or minimally invasive microneedle array that may be used in conjunction with a standard vacuum pump. Levels of these medications and their metabolites will then be detected and quantitated in these samples using standard and well-established instrumental analysis for comparison to blood samples.

Aim 1: Detect and quantitate buprenorphine and norbuprenorphine in ISF collected from the surface of the skin using a minimally invasive microneedle array. ISF collected from the surface of the skin will be tested for buprenorphine (i.e., Suboxone®, Subutex®), norbuprenorphine (a metabolite of buprenorphine), and B3G (a metabolite of buprenorphine) using standard instrumental analysis.

Aim 2: Detect and quantitate methadone in ISF collected from the surface of the skin using a minimally invasive microneedle array. ISF collected from the surface of the skin will be tested for methadone and EDDP using standard instrumental analysis.

Aim 3: Establish correspondence between detected medication levels in ISF and blood. Medication levels for buprenorphine and methadone detected in the ISF will be compared to medication levels measured in blood samples for the purpose of understanding the correlation between the ISF and blood levels.

C. Background of the Study

Substance misuse is an immense problem for our society today, with heavy costs due to lost work productivity, health care needs, and judicial system expenses, as well as significant human costs in terms of lost lives, broken families, and unfulfilled personal potential. Substance use disorders (SUDs) are estimated to cause over $400 billion worth of monetary damage to the US economy on an annual basis.[1] The number of deaths related to drug overdose has more than quadrupled over the last decade from approximately 16,000 in 2006 to more than 70,000 in 2019, of which 36,359 were from an opioid overdose.[2] An opioid use disorder (OUD) is typically a chronic, relapsing illness, associated with significantly increased rates of morbidity and mortality**.** With the rising overdose deaths and more than 3 million US citizens and more than 16 million citizens worldwide suffering from OUD, opioid overdose was declared a national emergency in the United States in 2017.[3]

Current treatment strategies are not keeping pace with the growing opioid crisis, and new solutions are urgently needed, particularly given the high relapse rates in those with an OUD.[4] Patients who have a previous history of

overdose,[5] who have been recently discharged from detoxification programs,[6] or who are initiating or ending opioid maintenance therapy[7] tend to be at a high risk of an opioid overdose.

Buprenorphine (i.e., Suboxone®, Subutex®) and methadone are two medications that have been approved to treat OUD by the US Food and Drug Administration and have demonstrated the greatest opportunity for expanding access to patients in need.[8] Improvements in prescribing medications for opioid use disorders (MOUDs), through clinical practice guidelines and continuous monitoring could ensure safer, more effective treatment options for patients while reducing opioid misuse, overdose, and death.

Interstitial fluid (ISF) acts as a bridge between blood and cells and is one of the most prevalent and accessible fluids in the body.[9] Seventy five percent of ISF is made up of extracellular fluid and about 15-25% of body weight.[10] The local tissue biomarkers in ISF can be used to extract information about cellular and tissue physiology.[11] ISF contains information similar to plasma[12,13] and distinct biomarkers not found in plasma.[14]

ISF has been used for continuous glucose monitoring,[15] the determination of dermatologic drug bioavailability,[16] cancer tumor microenvironment analysis,[17] and more recently to detect caffein.[10] ISF can be collected via a microneedle patch,[18] biopsy,[19] suction blisters,[20] microdialysis and open-flow microperfusion,[21,22] reverse iontophoresis,[23] and implantable biosensors.[15] These types of approaches require medical expertise, can be painful, can lead to scarring, infection or biofouling, and collects a mixture of extracellular ISF and intracellular material.[10]

A recent study developed a minimally invasive, microneedle-based method to sample ISF from human skin that was well tolerated by participants.[10] Through the use of a microneedle patch, an array of micropores in the skin coupled with mild suction was used in 21 human participants to sample ISF and identify distinct biomarkers.[10] These ISF samples were then compared to companion plasma samples based on mass spectrometry analysis.[10] The results from the study showed that many biomarkers used in research and current clinical practice were common to ISF and plasma.[10] A benefit to using ISF includes its inability to clot, which allows the continuous monitoring of these biomarkers in the ISF.[10] This approach resembles the continuous glucose monitors but without the need for an indwelling subcutaneous sensor.[10] The aforementioned study determined that ISF and plasma demonstrated similar pharmacokinetics of caffeine in healthy adults and pharmacodynamics of glucose in children and young adults with diabetes.

Another study developed a new multimodal microneedle sensor array which relies on unmodified and organophosphorus hydrolase (OPH) enzyme-modified carbon paste (CP) microneedle electrodes for square wave voltammetric (SWV) detection of the fentanyl (a type of opioid) and nerve agent targets, respectively.[24] The patch developed in this aforementioned study is capable of continuously monitoring fentanyl down to the nanomolar level through a nanomaterial-based multilayered surface architecture.[24]

The purpose of this study is to determine if buprenorphine, methadone, and their metabolites (i.e., norbuprenorphine [a metabolite of buprenorphine], B3G [a metabolite in buprenorphine], and EDDP [a metabolite for methadone]), can be detected in ISF. To achieve these aims, very small volumes of ISF from the surface of the skin will be collected from patients with a prescription for one of these medications using tiny needles with a standard vacuum pump. These medications and their metabolites will then be detected and quantitated in these samples using standard and well-established protocols for HPLC-MS or HPLC-MS-MS instrumental analysis for comparison to blood samples. Blood samples will be collected to compare what is in the ISF to what is in the blood. Information learned in this pilot study will be used to develop a sensor, which can be used for monitoring of these medications in humans. A continuous medication monitoring monitor could ensure safer, more effective treatment options for patients while reducing misuse, overdose, and death.

PARTICIPANT SELECTION

B. Inclusion and Exclusion Criteria: 3 groups (total n=22)

- Buprenorphine (e.g., Subutex®) or buprenorphine/naloxone (e.g., Suboxone®; n=10)
- Methadone (n=10)
- Controls (n=2)

Aim 1: Buprenorphine group (n=10):

- **Inclusion criteria for buprenorphine group includes:**
  - Age 18-65.
  - A prescription for sublingual buprenorphine or buprenorphine/naloxone at dose ≥ 16mg/4mg
  - Taken buprenorphine or buprenorphine/naloxone as prescribed in the last 7 days.

- **Exclusion criteria for buprenorphine group includes:**
  - Age <18 or >65.
  - A condition preventing or complicating ISF collection. Conditions may include dermatological (skin) condition, immunodeficiency, recent blood donation, anemia, cancer, congestive heart failure, HIV, Hepatitis C [HCV], or tuberculosis [TB].
  - Any active severe depression (e.g., suicidal ideation) or mania symptoms.
  - Lactation, pregnancy, or intending to become pregnant during the course of the study.
  - Alcohol use in the past 7 days.
  - Illicit substance use in past 7 days (e.g., heroin, methamphetamines).
  - Under a conservatorship.

Aim 2: Methadone group (n=10):

- **Inclusion criteria for methadone group includes:**
  - Age 18-65.
  - A prescription for liquid methadone at dose ≥ 60mg.
  - Taken methadone as prescribed in the last 7 days.

- **Exclusion criteria for methadone group includes:**
  - Age <18 or >65.
  - A condition preventing or complicating ISF collection. Conditions may include dermatological (skin) condition, immunodeficiency, recent blood donation, anemia, cancer, congestive heart failure, HIV, HCV, or TB. Any active severe depression (e.g., suicidal ideation) or mania symptoms.
  - Lactation, pregnancy, or intending to become pregnant during the course of the study.
  - Alcohol use in the past 7 days.
  - Illicit substance use in past 7 days (e.g., heroin, methamphetamines).
  - Under a conservatorship.

Aim 3: **Establish correspondence between ISF & Blood (n=22):**

- **Inclusion criteria for this group includes:**
  - Age 18-65.
  - A prescription for buprenorphine at dose ≥ 16 mg/4mg, a prescription for buprenorphine/naloxone at dose ≥ 16 mg/4mg, a prescription for methadone at dose ≥ 60mg, or part of the control group.
  - Taken buprenorphine, buprenorphine/naloxone, or methadone as prescribed in the last 7 days, or part of the control group.

- **Exclusion criteria for this group includes:**
  - Age <18 or >65.
  - A condition preventing or complicating ISF collection. Conditions may include schizophrenia, bipolar, depression, dermatological (skin) condition, immunodeficiency, recent blood donation, anemia, cancer, congestive heart failure, HIV, HCV, or TB.
  - Any active severe depression (e.g., suicidal ideation) or mania symptoms.
  - Lactation, pregnancy, or intending to become pregnant during the course of the study.
  - Alcohol use in the past 7 days.
  - Illicit substance use in past 7 days (e.g., heroin, methamphetamines).
  - Under a conservatorship.

Control Group (n=2):

- **Inclusion criteria for control group includes:**
  - Age 18-65.

- **Exclusion criteria for control group includes:**
  - Age <18 or >65
  - Prescription for opioid medications (e.g., buprenorphine, buprenorphine/naloxone, methadone)
  - Have not taken any opioids agonist medications (e.g., buprenorphine, buprenorphine/naloxone, methadone) in the last 7 days.
  - A condition preventing or complicating ISF collection. Conditions may include schizophrenia, bipolar, depression, dermatological (skin) condition, immunodeficiency, recent blood donation, anemia, cancer, congestive heart failure, HIV, HCV, or TB.
  - Any active severe depression (e.g., suicidal ideation) or mania symptoms.
  - Lactation, pregnancy, or intending to become pregnant during the course of the study.
  - Alcohol use in the past 7 days.
  - Illicit substance use in past 7 days (e.g., heroin, methamphetamines).
  - Under a conservatorship.

B. Sex
Equal inclusion of both men (n= 11) and women (n= 11) will be included to ensure the equitable sharing of both the potential risks, and the potential benefits that may result from this research. Women of childbearing potential are eligible to participate in this study. Acceptable methods of birth control include abstinence, meaning a total lack of any sexual activity, as well as the use of oral contraceptives (the "pill"), contraceptive injections, intrauterine device, double-barrier method (diaphragm or condom + spermicidal cream), contraceptive patch, or male partner sterilization. Pregnant women will not be included.

C. Racial/Ethnic Origin
There will be no racial/ethnic enrollment restrictions in this pilot study.

D. Vulnerable Populations
Vulnerable populations such as pregnant women, children, fetuses, wards of the state, severely cognitively impaired individuals, as well as prisoners and institutionalized individuals will not be included in this pilot study.

E. Age
Subjects under the age of 18 will not be included in this study. Older adults are known to metabolize substances differently, as such those over 65 will also not be included in this study.

F. Total Number of Participants to be Enrolled

As seen in a similar study sampling ISF to identify and compare clinically relevant and distinct biomarker composition, up to 22 subjects will be enrolled in this study.[10]

STUDY DESIGN / METHODS / PROCEDURES

We will conduct a non-randomized, non-blinded, feasibility study at a single center in the United States. The study will include a total of 10 male and 10 female adults (ages 18–65) who have a prescription for buprenorphine, buprenorphine/naloxone, or methadone and 1 male and 1 female adult control participants (total n=22).

A. Summary of the Research Design

Subject Recruitment Strategy: Up to 18 adults ages 18-65 years of age will be recruited to participate in this study. Subjects will be recruited from addiction medicine clinics through provider referrals (e.g., El Dorado Community Service Centers). Human subjects research will be performed at Synergy Research Centers (https://www.synergyresearchcenters.com) in San Diego which is a well-established clinical trial company that provides appropriate staff and facilities to conduct this study.

Study Procedures: The study consists of a 1) pre-screening phone call, 2) online assessment, 3) an in-person baseline clinical visit which will include a urine toxicology test, urine pregnancy test, pre blood sample, ISF extractions, and post blood sample, and 4) a post-ISF extraction follow-up call approximately 2 days after baseline visit. As such, there will only be one in-person visit.

- **Screening (up to 10 minutes)**
    a. Potentially eligible subjects will be identified by the research team and clinical staff through addiction medicine clinic referrals. The screening process may occur in-person or online. However, subjects will use an online screening process in both situations.
    b. Study eligibility will be conducted by the clinical research coordinator (CRC). See the supplemental material for specific questions.

- **Consent (up to 10-30 minutes):**
    a. If the potential subjects meet the inclusion criteria, does not meet the exclusion criteria, and agrees to learn more about the study, the CRC will send the study consent document link via an online Good Clinical Practice (GCP) compliant program to the subject for review.
    b. The CRC will walk the subjects through the consent and answer any questions the subject might have. As such, there will be no paper consents.

- **Initial questionnaire (up to 15-30 minutes):**
    a. If the potential subjects agree to participate as indicated by their online signature on the consent, they will be assigned a computer-generated Subject ID code and will be asked to complete the online baseline questionnaire in a GCP compliant data collection program (see the supplemental material for specific questions).

    b. The questionnaire will include the following:
        i. Demographics (e.g., age, sex, race, ethnicity)
        ii. Past and current diseases or medical conditions
        iii. Previous operations or medical procedures
        iv. Any medicines, vitamins, minerals, and herbal remedies that the person is currently taking
        v. Diet and exercise habits
        vi. Tobacco, alcohol and other substance use history
        vii. Previous pregnancy history (if female)
    c. The CRC will schedule an in-person clinical visit for the subjects if needed. Subjects will be instructed to take their medications as prescribed by their physician (e.g., dose, dosing times). As

such, the in-person visits will be scheduled around the subjects usual dosing time. For the control group, in-person assessments may occur at any time during the available clinic hours. Subjects will also be asked to abstain from alcohol and non-prescribed substances at least 24 hours before their in-person assessment.

- **In-person study visit within 7 days after the consent and online assessment is completed:**
  - **a. Physical assessment (up to 30 minutes)**
    - i. The in-person assessment may include the following:
      1. Limited physical exam:
         a. Height and weight measurements
         b. Feeling for the pulse
         c. Listening to the heart and lungs with a stethoscope
         d. Measuring blood pressure using a sphygmomanometer
      2. Changes in medications in the past week
      3. Use of substances (e.g., opioids, alcohol) in the past week
      4. Urine toxicology test which will test for the following substances: barbiturates, benzodiazepines, amphetamine, methamphetamines, cocaine, heroin, oxycodone, or other opiates. Subjects will be discharged from the study if they test positive for any of the listed non-prescribed medications tested and they will be paid a total of $50.
      5. Urine pregnancy test for premenopausal women. Subjects to be discharged if they test positive, paid $50, and referred to their primary care doctor or OBGYN.

  - **b. First blood sample collection (up to 10 minutes)**

    Immediately before the patient takes their prescribed medication, a standard venipuncture blood sample will be collected by a certified clinician. This sample will be used for comparative analysis with the ISF sample. For those in the control group, this will occur immediately after the physical assessment is completed.

  - **c. First Microneedle ISF collection (up to 1 hour)**
    - i. ISF will be collected by a board-certified physician with procedural skills, training, and familiarity with ISF collection. ISF collection will follow collection practices as described below and applied elsewhere.[10] The first ISF collection will occur immediately before the participant takes their prescribed medication. A subsequent collection will occur at the medication peak (e.g., 2-4 hours after medication administration; see below).
    - ii. ISF will be collected from the surface of the right or left arm (subject preference).
    - iii. The subject will be prepared for the ISF collections using standard clean working techniques (e.g., prepped and draped).
    - iv. The procedures will involve covering the skin with a transparent film skin dressing (e.g., Tegaderm) containing a 1-cm-diameter opening where microneedle treatment will be performed.
    - v. A minimally invasive microneedle array will be used in conjunction with a standard vacuum pump. Microneedles (without the patch) will be inserted and removed multiple times (~10) to collect about ≥ 1 µ1 of ISF. This approach has been well tolerated with faint visual evidence of micropores in the skin in a previous study.[10] A standard vacuum pump will then be administered at −50 kPa at room temperature for 20 min to draw out the ISF. Skin appearance should remain largely unchanged and result in a swift recovery as seen in a previous study.[10] Commercially available gauze will then be used to collect the ISF from the surface of the skin.

vi. After the ISF collection is complete, a sterile bandage covering will be supplied to the area.
vii. Subjects will be monitored after each ISF collection for up to 30 minutes and be asked to report their tolerability, pain, and experience. Their responses will be documented in a secure GCP certified online storage medium.
viii. This process will also occur for the control group. Because the control group will not be administered a medication, the timing of the blood and ISF collection will occur after physical assessment and 2-4 hours after the first collection.

d. Prescribed dose of medication (5 minutes)
i. Participants will be asked to take their prescribed oral medication at the study site. Study personnel may observe.

e. Second Microneedle ISF collection (up to 1 hour)
i. A second ISF collection will occur at the medication peak (e.g., 2-4 hours after medication administration). The ISF collection process described previously will be employed.

f. **Second blood sample collection (10 minutes)**
i. After the second ISF collection, a standard venipuncture blood sample will be collected by a certified clinician. This sample will be used for comparative analysis with the ISF samples.

- **Method of sample preservation**
  a. Blood samples will be centrifuged and kept in the refrigerator.
  b. ISF samples will be stored at -80C and transported to the laboratory in a dry ice container.
  c. All samples will be transported to the laboratory within 24 hours of collection.

- **Follow-up call/visit (15 minutes)**
  a. Approximately 2 days after ISF collection, subjects will be contacted by the CRC via phone. Subjects will be asked to report their tolerability, pain, and experience. Their responses will be documented in a secure an online storage medium.

- **Compensation:** Subjects will be compensated with an online visa gift card worth up to $250 for their participation in this study. Participants will be compensated $25 for the initial online assessment (up to 15-30 minutes), $30 for the in-person physical exam and data collection (up to 30 minutes), $10 for the first pre ISF collection blood (up to 10 minutes), $150 for two ISF collection and monitoring (2 collections up to 60 minutes each [$75 each]), $10 for the post ISF collection blood collection (up to 10 minutes each), and $25 for the follow-up call (up to 15 minutes).

All the biological samples collected in this study (e.g., ISF, blood; about 2ml per sample) will be tested for the subject's prescribed medications and their metabolites at a laboratory that has experience with these types of samples (e.g., Expert Chemical Analysis (*ECA*); http://ecalab.com/). Urine will be tested for illicit substances to inform eligibility.

There will be no paper data stored in locked filing cabinets or offices. A unique subject ID code will be created in analytic databases and be used to link all data in an individual file because such linkage is critical for communication with the subject. Research data will be separated from identifying data. All data will be stored on secure password protection servers. Data from this study will be transferred from the secure online service electronically, and stored on secure servers. The research sites used in this study have well established systems for protection of confidential subject information. All computers and files containing confidential information will be password protected and monitored by study staff. As such, the data will be limited to a small number of project

investigators and research staff. Backups of electronic data stored in a secure cloud-based location will be maintained at all times.

B. Analysis of Study Results

ISF and blood samples from up to the 22 participants will be analyzed using standard instrumental chemical analysis protocols. The analyses will be conducted by a professional service laboratory, such as ECA, which specializes in the detection and quantitation of controlled substances in bodily fluids. Levels of these medications and their metabolites will then be detected and quantitated in these samples using standard and well-established instrumental analysis for comparison to blood samples. Published protocols will be followed for quantitation of buprenorphine, methadone, and their respective metabolites.

C. Monitoring

N/A

D. Storage of Data

The original electronically signed consent forms will be stored in a secure password protected file on the study computer. Only the research team members (Principal Investigators/Co-Investigators) and the CRCs will have access to identifiable private information about the human subjects.

An electronic data sheet casebook using GCP certified software will be used for each subject enrolled in the study. The appropriate data sheet will be completed online by the CRCs after each visit. All data collected for the study will be reviewed for quality assurance, data entry, and statistical analysis. All electronic forms will be reviewed for completeness; evident recording errors will be rectified by contact with the appropriate clinical staff. All data sheets will be reviewed by a research team member before final data entry submission. Data will be entered within two (2) weeks of a subject's visit. Any corrections will be made electronically.

All biological samples will be stored and processed through standard IRB approved procedures. Subjects will consent to allow their deidentified biological samples to be stored for future use.

All team members will be GCP certified and trained to protect identifiable private information (e.g., signed consent). Deidentified research data will be kept separate from identifiable data in secure GCP certified online locations for the duration of the study. This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of GCP regulations. These requirements are stated in global regulations as well as "Guidance for Good Clinical Practice," International Conference on Harmonization (ICH), and the most recent guidelines of the Declaration of Helsinki of Technical Requirements for Registration of Pharmaceuticals for Human Use.

E. Confidentiality of Data

Due to the sensitivity of the health information, strict precautions will be employed to protect confidentiality. Subjects will be informed that their participation in the study is voluntary and they may choose to not participate or withdraw from the study at any time without prejudice or loss of benefits to which they are otherwise entitled. All study personnel will be compliant with GCP regulations.

Risks associated with confidentiality will be minimized by collecting and storing data securely. There will be no paper data stored in locked filing cabinets or offices. A unique Subject ID code will be created in analytic databases.

The unique Subject ID code will be used to link all data in an individual file because such linkage is critical for communication with the subject. Research data will be separated from identifying data. All data will be stored on secure servers using password protection. Data from this study will be transferred from the secure online service electronically, and stored on secure servers. All bio-samples will be labeled with the subject's ID number. As such, no identifying information will be listed on the bio-samples. All computers and files containing confidential information will be password protected and monitored by study staff. The data will be limited to a small number of project investigators and research staff. Backups of electronic data stored in a secure cloud-based location will be maintained at all times.

RISK/BENEFIT ASSESSMENT

A. Risks

The most important risks or discomforts that subjects may expect from taking part in this research include mild allergic reaction to adhesives, bleeding, bruising, infection, pain or discomfort, scarring or skin discoloration, skin inflammation, thinning, discoloration and/or redness. Although unlikely, hospitalization due to infection is possible. Based on clinical studies and post market data available for a similar approach, it is expected that the occurrence of any adverse events will be low.

As with most research involving human subject, loss of confidentiality or breach of privacy is a risk. The proposed study involves data collected over the internet and in person. Data will be transferred to and from the online data system electronically, and stored on secure servers through Synergy Research Centers.

B. Prevention of Risks

Only board-certified physicians with procedural skills and training and familiarity with ISF collection will collect the ISF. Study staff will monitor subjects for any adverse events described in the next section. The CRA will also contact the subjects two days after the procedure to assess their tolerability, pain, and experience. All potential adverse events will be assessed and reported when necessary.

As mentioned, risks associated with confidentiality will be minimized by collecting and storing data securely. There will be no paper data (e.g., test forms) stored in locked filing cabinets/offices. A unique subject code will be created in analytic databases, as mentioned. The unique Subject ID code will be used to link all data in an individual file because such linkage is critical for data analyses. Research data will be separated from identifying data. All data will be stored on secure servers using password protection. Data from this study will be transferred from the secure online service electronically, and stored on secure servers. All computers and files containing confidential information will be password protected and monitored by study staff. As such, the data will be limited to a small number of project investigators and research staff. Backups of electronic data stored in a secure cloud-based location will be maintained at all times.

C. Adverse Events

Below is a list of the potential adverse effects (e.g., complications) associated participating in this study:

- Mild allergic reaction to adhesives
- Mild bleeding
- Mild bruising
- Mild or moderated infection
- Mild or moderate pain or discomfort
- Mild scarring or skin discoloration
- Mild skin inflammation, thinning, discoloration and/or redness.

- Although unlikely, hospitalization due to infection is possible.

D. Benefits

Besides the financial compensation outlined in this protocol, there is no immediate personal benefit to the subjects. However, it is believed that these research efforts will lead to significantly improved responses to the growing opioid epidemic. Relevant information learned in this study will be managed with care and in a respectful manner. Strict protection over subject information to ensure confidentiality will be employed.

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